Complete Summary

GUIDELINE TITLE

2001 consensus guidelines for the management of women with cervical cytological abnormalities.

BIBLIOGRAPHIC SOURCE(S)

Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA 2002 Apr 24;287(16):2120-9. [89 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

- Atypical squamous cells of undetermined significance (ASC-US)
- Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion (HSIL) (ASC-H)
- Cervical intraepithelial neoplasia (CIN) grade 1 (low-grade precursors) or grade 2,3 (high-grade precursors)
- Atypical glandular cells, either endocervical, endometrial, or "glandular cells" not otherwise specified (AGC-NOS)
- Atypical glandular cells, either endocervical or "glandular cells" favor neoplasia (AGC "favor neoplasia")
- Endocervical adenocarcinoma in situ (AIS)
- Low-grade squamous intraepithelial lesion (LSIL)
- High-grade squamous intraepithelial lesion (HSIL)
- Cervical cancer

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Prevention
Screening
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Obstetrics and Gynecology
Oncology
Pathology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Plans
Managed Care Organizations
Physician Assistants
Physicians
Public Health Departments

GUIDELINE OBJECTIVE(S)

- To provide evidence-based consensus guidelines for the management of women with cervical cytological abnormalities and cervical cancer precursors
- To update the 1996-1997 guidelines issued by the American Society of Colposcopy and Cervical Pathology on atypical squamous cells of undetermined significance (ASC-US) [Colposcopist 1996 Winter; 27(1):1-9]; endocervical curettage [J Lower Genital Tract Disease 1997;1(4):251-6]; glandular abnormalities in the cervical smear [J Lower Genital Tract Disease 1997;1(1):41-5]; and quality of the cervical smear [J Lower Genital Tract Disease 1997;1(2):100-6]

TARGET POPULATION

Women with cervical cytological abnormalities and cervical cancer precursors

INTERVENTIONS AND PRACTICES CONSIDERED

Atypical squamous cells (ASC) management

1. Repeat cervical cytology testing (conventional or liquid-based)
2. Colposcopy
3. Human papillomavirus (HPV) DNA testing
4. Combining single repeat cervical cytological testing with adjunctive method

Atypical glandular cells (AGC) and adenocarcinoma in situ (AIS) management

1. Colposcopy with endocervical sampling
2. Endometrial sampling
3. Diagnostic excisional procedure, such as cold-knife conization
4. Repeat cervical cytological testing

Low-grade squamous intraepithelial lesion (LSIL) management

1. Colposcopy
2. Endocervical sampling
3. Repeat cervical cytological testing
4. Human papillomavirus DNA testing
5. Intravaginal estrogen followed by repeat cervical cytology

High-grade squamous intraepithelial lesion (HSIL) management

1. Colposcopy with endocervical assessment
2. Review of cytology, colposcopy, and histology results
3. Diagnostic excisional procedure (in non-pregnant patients only)

   [Note: Endocervical curettage is unacceptable in pregnant women.]

4. Repeat cytology and colposcopy, as needed

MAJOR OUTCOMES CONSIDERED

- Sensitivity and specificity of testing (Papanicolaou, colposcopy, human papillomavirus [HPV], cervical cytology, endocervical sampling)
- Cervical intraepithelial neoplasia (CIN) grade

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed searches of the U.S. Library of Medicine´s MEDLINE database for English-language articles published between 1988 and 2001. Abstracts of articles were reviewed to determine their relevance; relevant articles were reviewed to determine whether they fulfilled a minimum, pre-determined scientific standard. In instances in which published data pertaining to a key issue were missing, scant, or conflicting, expert opinions expressed on an

open Internet bulletin board or by members of the working group were used to help formulate the guidelines.

In addition to electronic searches, experts (committee members) were queried to identify studies not listed in MEDLINE, such as those in the Journal of Lower Genital Tract Disease. Also important to note that conference participants also introduced data and expert opinion. This was especially the case for then-unpublished NCI Atypical Squamous Cells of Undetermined Significance/Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) data.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of Evidence

I. Evidence from at least one randomized controlled trial.
II. Evidence from at least one clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Abstracts of articles were reviewed to determine whether they fulfilled a minimum, predetermined scientific standard.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

From September 6 through 8, 2001, the American Society for Colposcopy and Cervical Pathology (ASCCP) hosted a consensus conference in Bethesda, MD, to develop evidence-based guidelines for the management of women with cervical

cytological abnormalities and cervical cancer precursors. To ensure that the guidelines reflect the needs of the diverse array of clinicians providing cervical cancer screening, the consensus conference included representatives from 29 participating professional and health organizations and federal agencies. Input from the professional community at large was obtained using a novel approach that incorporated Internet-based discussion groups.

At the consensus conference, guidelines were discussed together with the supporting data, revised if necessary, and voted upon. All guidelines were accepted by a minimum of a two-thirds majority vote.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Draft guidelines were posted on the Internet bulletin boards for public comment. At the consensus conference, guidelines were discussed together with the supporting data, revised if necessary, and voted upon. All guidelines were accepted by a minimum of a two-thirds majority vote. Multiple iterations of the revision/review process were allowed at the meeting.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Excerpted by the National Guideline Clearinghouse (NGC)

The ratings of the strength of recommendation (A-E), the quality of the evidence (I-III), and terminology used by the consensus conference (recommended, preferred, acceptable, unacceptable) are repeated at the end of the Major Recommendations.

The guideline uses the 2001 Bethesda System for cytological classification that uses the terms low-grade intraepithelial lesion (LSIL) and high-grade intraepithelial lesion (HSIL) to refer to cervical cancer precursors. The guideline developers adopted a two-tiered terminology for the histopathological classification of cervical intraepithelial neoplasia (CIN): CIN 1 denotes low-grade precursors and CIN 2,3 denotes high-grade precursors.

Atypical Squamous Cells (ASC)

The 2001 Bethesda System subdivides atypical squamous cells (ASC) into 2 categories: atypical squamous cells of undetermined significance (ASC-US) and atypical squamous cells, cannot exclude HSIL (ASC-H). Several considerations underlie the consensus guidelines for the management of ASC. First, even among expert cytologists, the interpretation of a cervical cytology result as ASC is poorly reproducible. Second, a woman with a cervical cytology result interpreted as ASC has a 5% to 17% chance of having CIN 2,3 confirmed by biopsy, while CIN 2,3 is identified in 24% to 94% of those with ASC-H. However, the risk of invasive cervical cancer in a woman with ASC is low (approximately 0.1% to 0.2%). These considerations suggest that a woman with ASC requires some form of additional workup or follow-up, but that consideration should be given to preventing unnecessary inconvenience, anxiety, cost, and discomfort. Immunosuppressed women with ASC are at increased risk for CIN 2,3, and high-risk types of human papillomavirus (HPV) are frequently detected in immunosuppressed women, suggesting that these women require special consideration. Conversely, postmenopausal women with ASC appear to be at lower risk for CIN 2,3 than premenopausal women.

Recommended Management of Women With ASC-US

A program of repeat cervical cytological testing, colposcopy, or DNA testing for high-risk types of HPV are all acceptable methods for managing women with ASC-US (rating AI). When liquid-based cytology is used or when co-collection for HPV DNA testing can be done, reflex HPV DNA testing is the preferred approach (AI).

DNA testing for high-risk types of HPV should be performed using a sensitive molecular test, and all women who test positive for HPV DNA should be referred for colposcopic evaluation (AII). Women with ASC-US who test negative for high-risk HPV DNA can be followed up with repeat cytological testing at 12 months (BII). Acceptable management options for women who are positive for high-risk types of HPV, but who do not have biopsy-confirmed CIN, include follow-up with repeat cytological testing at 6 and 12 months with referral back to colposcopy if a result of ASC-US or greater is obtained, or HPV DNA testing at 12 months with referral back to colposcopy of all HPV DNA–positive women (BII).

When a program of repeat cervical cytological testing is used, women with ASC-US should undergo repeat cytological testing (either conventional or liquid-based) at 4 to 6-month intervals until 2 consecutive "negative for intraepithelial lesion or malignancy" results are obtained (AII). Women diagnosed with ASC-US or greater cytological abnormality on the repeat tests should be referred for colposcopy (AII). After 2 repeat "negative for intraepithelial lesion or malignancy" cytology tests are obtained, women can be returned to routine cytological screening programs (AII).

When immediate colposcopy is used to manage women with ASC-US, women who are referred for colposcopy and found not to have CIN should be followed up with repeat cytological testing at 12 months (BII). Women with ASC-US who are referred for colposcopy and found to have biopsy-confirmed CIN should be managed according the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities.

Because of the potential for overtreatment, diagnostic excisional procedures such as the loop electrosurgical excision procedure (LEEP) should not routinely be used to treat women with ASC in the absence of biopsy-confirmed CIN (EII).

ASC-US in Special Circumstances

Postmenopausal Women. Providing a course of intravaginal estrogen followed by a repeat cervical cytology test obtained approximately a week after completing the regimen is an acceptable option for women with ASC-US who have clinical or cytological evidence of atrophy and no contraindications to using intravaginal estrogen (CIII). If the repeat test result is "negative for intraepithelial lesion or malignancy", the test should be repeated in 4 to 6 months. If both repeat cytological test results are "negative for intraepithelial lesion or malignancy", the patient can return to routine cytological screening, whereas if either repeat test result is reported as ASC-US or greater, the patient should be referred for colposcopy (AII).

Immunosuppressed Women. Referral for colposcopy is recommended for all immunosuppressed patients with ASC-US (BII). This includes all women infected with human immunodeficiency virus (HIV), irrespective of CD4 cell count, HIV viral load, or antiretroviral therapy.

Pregnant Women. It is recommended that pregnant women with ASC-US be managed in the same manner as nonpregnant women (BIII).

Recommended Management of Women With ASC-H

The recommended management of women with ASC-H obtained using either conventional or liquid-based cervical cytology is referral for colposcopic evaluation (AII).

When no lesion is identified after colposcopy in women with ASC-H, it is recommended that, when possible, a review of the cytology, colposcopy, and histology results be performed (CIII). If the review yields a revised interpretation, management should follow guidelines for the revised interpretation; if a cytological interpretation of ASC-H is upheld, cytological follow-up at 6 and 12 months or HPV DNA testing at 12 months is acceptable (CIII). Women who are found to have ASC or greater on their repeat cervical cytology tests or who subsequently test positive for high risk HPV DNA should be referred for colposcopy.

Atypical Glandular Cells (AGC) and Adenocarcinoma In Situ (AIS)

The 2001 Bethesda System classifies glandular cell abnormalities less severe than adenocarcinoma into 3 categories: atypical glandular cells, either endocervical, endometrial, or "glandular cells" not otherwise specified (AGC NOS); atypical glandular cells, either endocervical or "glandular cells" favor neoplasia (AGC "favor neoplasia"); and endocervical adenocarcinoma in situ (AIS).

The atypical glandular cells (AGC) category is associated with a substantially greater risk for cervical neoplasia than the ASC or LSIL categories. Various studies

have found that 9% to 54% of women with AGC have biopsy-confirmed CIN, 0% to 8% have biopsy-confirmed AIS, and less than 1% to 9% have invasive carcinoma. The 2001 Bethesda System separated AGC NOS from AGC "favor neoplasia" because it was believed that these 2 categories represent women at different risk for having significant disease, either squamous or glandular. Although the risk of having a high-grade lesion in various studies overlap, studies from individual centers have usually reported a higher risk among women with AGC "favor neoplasia" than among those with AGC NOS. Biopsy-confirmed high-grade lesions including CIN 2,3, AIS, or invasive cancer have been found in 9% to 41% of women with AGC NOS compared with 27% to 96% of women with AGC "favor neoplasia". The cytological interpretation of AIS is associated with a very high risk of a woman having either AIS (48%-69%) or invasive cervical adenocarcinoma (38%).

Recommendations for Managing Women With AGC or AIS

Initial Evaluation. Colposcopy with endocervical sampling is recommended for women with all subcategories of AGC, with the exception that women with atypical endometrial cells should initially be evaluated with endometrial sampling (AII). Endometrial sampling should be performed in conjunction with colposcopy in women older than 35 years with AGC and in younger women with AGC who have unexplained vaginal bleeding (AII). Colposcopy with endocervical sampling is also recommended for women with a cytological test result of AIS. Management of women with initial AGC or AIS using a program of repeat cervical cytological testing is unacceptable (EII). Currently, there are insufficient data to allow an assessment of HPV DNA testing in the management of women with AGC or AIS (CIII).

Subsequent Evaluation or Follow-up. If invasive disease is not identified during the initial colposcopic workup, it is recommended that women with AGC "favor neoplasia" or endocervical AIS undergo a diagnostic excisional procedure (AII). The preferred diagnostic excisional procedure for women with AGC or AIS is cold-knife conization (BII). If biopsy-confirmed CIN (of any grade) is identified during the initial workup of a woman with AGC NOS, management should be according to the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities. If no neoplasia is identified during the initial workup of a woman with AGC NOS, it is recommended that the woman be followed up using a program of repeat cervical cytological testing at 4- to 6-month intervals until 4 consecutive "negative for intraepithelial lesion or malignancy" results are obtained, after which the woman may return to routine screening (BIII). If a result of either ASC or low-grade squamous intraepithelial lesion (LSIL) is obtained on any of the follow-up Papanicolaou tests, acceptable options include a repeat colposcopic examination or referral to a clinician experienced in the management of complex cytological situations (BIII).

Low-Grade Squamous Intraepithelial Lesion

In 1996 the median rate of occurrence of LSIL in the United States was 1.6%, but laboratories serving high-risk populations report LSIL rates as high as 7.7%. Cytological grade is a relatively poor predictor of the grade of CIN that will be identified at colposcopy, and approximately 15% to 30% of women with LSIL on cervical cytology will have CIN 2,3 identified on a subsequent cervical biopsy.

Recommendations for Managing Women With LSIL

Colposcopy is the recommended management option for women with LSIL (AII). Subsequent management options depend on whether a lesion is identified, whether the colposcopic examination is satisfactory, and whether the patient is pregnant. The routine use of diagnostic excisional procedures such as loop electrosurgical excision procedure or ablative procedures is unacceptable for the initial management of patients with LSIL in the absence of biopsy-confirmed CIN (DII).

Satisfactory Colposcopy. Endocervical sampling is acceptable for nonpregnant women with satisfactory colposcopic findings and a lesion identified in the transformation zone (CII), but it is preferred for nonpregnant women in whom no lesions are identified (BII). If biopsy, with or without endocervical sampling, fails to confirm CIN and the colposcopy is satisfactory, acceptable management options include follow-up with repeat cytological testing at 6 and 12 months with a referral for colposcopy if a result of ASC-US or greater is obtained, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive for a high-risk type of HPV (BII).

Unsatisfactory Colposcopy. Endocervical sampling is preferred for nonpregnant women with unsatisfactory colposcopic findings (BII). If biopsy fails to confirm CIN and the colposcopy is unsatisfactory, acceptable management options include follow-up with repeat cytological testing at 6 and 12 months with a referral for colposcopy if a result of ASC-US or greater is obtained, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive (BII).

Women with LSIL who are found to have biopsy-confirmed CIN should be managed according to the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities.

LSIL in Special Circumstances

Postmenopausal Women. In postmenopausal patients, follow-up without initial colposcopy is an acceptable option using protocols of either follow-up with repeat cytological testing at 6 and 12 months with a threshold of ASC-US or greater for referral for colposcopy, or follow-up with HPV DNA testing at 12 months with referral for colposcopy if testing is positive (CIII).

A course of intravaginal estrogen followed by a repeat cervical cytology test approximately a week after completing the regimen is acceptable for women with LSIL who have clinical or cytological evidence of atrophy, with a referral for colposcopy if a result of ASC-US or greater is obtained and there are no contraindications to using intravaginal estrogen (CIII). If the repeat cervical cytology test result is "negative for intraepithelial lesion or malignancy", cytological testing should be repeated in 4 to 6 months. If both repeat cytology test results are "negative for intraepithelial lesion or malignancy", the patient can return to routine cytological screening, whereas if either repeat result is reported as ASC or greater, the patient should be referred for colposcopy (CIII).

Adolescents. In adolescents, an acceptable option is follow-up without initial colposcopy using a protocol of repeat cytological testing at 6 and 12 months with

a threshold of ASC for referral for colposcopy, or of HPV DNA testing at 12 months with a referral for colposcopy if testing is positive for high risk HPV DNA (CIII).

Pregnant Women. For the recommended management of pregnant women with a diagnosis of LSIL, see the "HSIL in Special Circumstances" section, below.

High-Grade Squamous Intraepithelial Lesion

A cytological diagnosis of high-grade squamous intraepithelial lesion (HSIL) is uncommon, accounting for only 0.45% of cytology interpretations in 1996. Women with a cytological diagnosis of HSIL have approximately a 70% to 75% chance of having biopsy-confirmed CIN 2,3 and a 1% to 2% chance of having invasive cervical cancer.

Recommendations for Managing Women With HSIL

Colposcopy with endocervical assessment is the recommended management of women with HSIL (AII). Subsequent management options depend on whether a lesion is identified, whether the colposcopic examination is satisfactory, whether the patient is pregnant, and whether immediate excision is appropriate.

Satisfactory Colposcopy. When no lesion or only biopsy-confirmed CIN 1 is identified after satisfactory colposcopy in women with HSIL, it is recommended that, when possible, a review of the cytology, colposcopy, and histology results be performed (BIII). If the review yields a revised interpretation, management should follow guidelines for the revised interpretation; if a cytological interpretation of HSIL is upheld or if review is not possible, a diagnostic excisional procedure is preferred in nonpregnant patients (BII). A colposcopic reevaluation with endocervical assessment is acceptable in special circumstances (see below) (BIII).

Unsatisfactory Colposcopy. When no lesion is identified after unsatisfactory colposcopy in women with HSIL, a review of the cytology, colposcopy, and histology results should be performed when possible (BIII). If the review yields a revised interpretation, management should follow guidelines for the revised interpretation. If a cytological interpretation of HSIL is upheld, review is not possible, or biopsy-confirmed CIN 1 is identified, a diagnostic excisional procedure is recommended in nonpregnant patients (AII). Ablation is unacceptable (EII).

Omission of endocervical sampling is acceptable when a diagnostic excisional procedure is planned. In women with HSIL in whom colposcopy suggests a high-grade lesion, initial evaluation using a diagnostic excisional procedure is also an acceptable option (BI). Triage using either a program of repeat cytological testing or HPV DNA testing is unacceptable (EII). Women with HSIL who are found to have biopsy-confirmed CIN should be managed according the 2001 Consensus Guidelines for the Management of Women With Cervical Histological Abnormalities.

HSIL in Special Circumstances

Pregnant Women. It is preferred that the colposcopic evaluation of pregnant women with HSIL be conducted by clinicians who are experienced in the evaluation of colposcopic changes induced by pregnancy (BIII). Biopsy of lesions suspicious for high-grade disease or cancer is preferred; biopsy of other lesions is acceptable (BIII). Endocervical curettage is unacceptable in pregnant women (EIII). Since unsatisfactory colposcopy may become satisfactory as the pregnancy progresses, it is recommended that women with unsatisfactory colposcopic findings undergo a repeat colposcopic examination in 6 to 12 weeks (BIII). In the absence of invasive disease, additional colposcopic and cytological examinations are recommended, with biopsy recommended only if the appearance of the lesion worsens or if cytology suggests invasive cancer (BII). Unless invasive cancer is identified, treatment is unacceptable (EII). A diagnostic excisional procedure is recommended only if invasion is suspected (BII). Reevaluation with cytology and colposcopy is recommended no sooner than 6 weeks postpartum (CIII).

Young Women of Reproductive Age. When biopsy-confirmed CIN 2,3 is not identified in a young woman with cytology-confirmed HSIL, observation with colposcopy and cytology at 4- to 6-month intervals for 1 year is acceptable, provided colposcopic findings are satisfactory, endocervical sampling is negative, and the patient accepts the risk of occult disease. If a lesion appears to progress to a colposcopic high-grade lesion or if HSIL cytology persists, a diagnostic excisional procedure is recommended (BIII).

Definitions:

Strength of Recommendation

A. Good evidence for efficacy and substantial clinical benefit support recommendations for use.
B. Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use.
C. Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use.

Quality of Evidence

I. Evidence from at least one randomized controlled trial.
II. Evidence from at least one clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Terminology*

Recommended: Good data to support use when only one option is available.

Preferred: Option is the best (or one of the best) when there are multiple other options.

Acceptable: One of multiple options when either there are data indicating that another approach is superior or when there are no data to favor any single option.

Unacceptable: Good data against use

*The assignment of these terms represents an opinion or vote by the consensus conference, and the assignment is not directly linked to the "strength of the recommendation" or the "quality of the evidence".

CLINICAL ALGORITHM(S)

Algorithms for the following are available from the American Society of Colposcopy and Cervical Pathology Web site:

- Management of women with atypical squamous cells of undetermined significance (ASC-US).
- Management of women with atypical squamous cells of undetermined significance (ASC-US) in special circumstances.
- Management of women with atypical squamous cells: cannot exclude high-grade SIL (ASC-H).
- Management of women with atypical glandular cells (AGC).
- Management of women with low-grade squamous intraepithelial lesions (LSIL).
- Management of women with low-grade squamous intraepithelial lesions (LSIL) in special circumstances.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

In instances in which published data pertaining to a key issue were missing, scant or conflicting, evidence brought to the meeting by the expert conference participants and expert opinions expressed on the Internet bulletin boards or by members of the working group were used to help formulate the guidelines.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Atypical squamous cells (ASC) management

- The advantage of colposcopy for the evaluation of women with atypical squamous cell (ASC) is that it immediately informs both the woman and the clinician of the presence or absence of significant disease. A metaanalysis of

the performance of colposcopy reported that the weighted mean sensitivity for distinguishing normal cervical tissue from abnormal tissue by colposcopy was 0.96 and the weighted mean specificity was 0.48.

- The sensitivity of human papillomavirus (HPV) DNA testing for the detection of biopsy-confirmed cervical intraepithelial neoplasia (CIN) 2,3 in women with atypical squamous cells is 0.83 to 1.0 and is higher than the sensitivity of a single repeat cervical cytological test (conventional or liquid-based) in all of the reported series. The negative predictive value of DNA testing for high-risk types of HPV is generally reported to be 0.98 or greater.
- "Reflex" HPV DNA testing is an alternate approach, in which the original liquid-based cytology specimens or a sample co-collected for HPV DNA testing at the initial screening visit is tested for HPV DNA only if an atypical squamous cell of undetermined significance (ASC-US) result is obtained. Reflex HPV DNA testing offers significant advantages since women do not need an additional clinical examination for specimen collection, and 40% to 60% of women will be spared a colposcopic examination. Moreover, women testing negative for HPV DNA can rapidly be assured that that they do not have a significant lesion.

Atypical squamous cells, cannot exclude HSIL (ASC-H) and low-grade squamous intraepithelial lesion (LSIL) management

Referring all women with atypical squamous cells, cannot exclude HSIL (ASC-H) or low-grade squamous intraepithelial lesion (LSIL) for colposcopy allows women with significant disease to be rapidly identified and would be expected to reduce the risk that women would be lost to follow-up.

High-grade squamous intraepithelial lesion (HSIL) management

The approach of managing nonpregnant women with high-grade squamous intraepithelial lesion (HSIL) by immediate loop electrosurgical excision procedure (LEEP) of the transformation zone (i.e., "see and treat") has been shown to be safe, efficacious, and cost-effective, particularly in the hands of expert colposcopists. However, most studies of women undergoing immediate loop electrosurgical excision procedure for cytological abnormalities have reported that a significant number of the excised specimens will lack histologically confirmed cervical intraepithelial neoplasia. Therefore this approach appears to be most appropriate for patients from populations at risk of loss to follow-up and for older patients in whom possible adverse effects of loop electrosurgical excision procedure on fertility are not an issue.

POTENTIAL HARMS

Atypical squamous cells (ASC) management

- Although repeat cytological testing is widely used for managing women with atypical squamous cells, the sensitivity of a single repeat test for detecting CIN 2,3 is relatively low (0.67-0.85).
- Repeating cervical cytological testing has several disadvantages compared with other management options. It can delay the diagnosis of cervical intraepithelial neoplasia (CIN) 2,3 or cervical cancer and, even in populations

with good access to health care, adherence to recommendations becomes a problem for any follow-up that requires multiple visits.
- The sensitivity of colposcopy in the published literature may be higher than would be observed in routine clinical practice. The disadvantages of colposcopy are that many women consider the procedure to be uncomfortable, referral for colposcopy may raise false concerns about cervical disease, it is expensive, and it has the potential for overdiagnosis and overtreatment.
- Requiring women to return for human papillomavirus (HPV) DNA testing or repeat cervical cytological testing is inconvenient and would be expected to increase cost
- Using HPV testing for ASC triage has the potential harm of requiring co-collection or use of liquid media, likely increasing cost. Diagnosis of a sexually transmitted infection (HPV) may have adverse psychological sequelae.

Atypical glandular cells (AGC) and adenocarcinoma in situ (AIS) management

Many cases of biopsy-confirmed AIS have had no observed colposcopic abnormalities, and even combinations of cytological testing and colposcopy can miss small endocervical adenocarcinomas and AIS localized in the endocervical canal. Although the sensitivity of endocervical sampling for the detection of glandular neoplasia localized in the endocervical canal is not well defined, many cases of biopsy-confirmed AIS have had no colposcopic abnormalities and in some series endocervical sampling has detected glandular neoplasia that was missed at colposcopy. The potential harms of cone biopsy are bleeding, organ injury, and reduced fertility.

Atypical squamous cells, cannot exclude HSIL (ASC-H) and low-grade squamous intraepithelial lesion (LSIL) management

- Approaches that previously have been recommended for managing women with atypical squamous cells, cannot exclude HSIL (ASC-H) or low-grade squamous intraepithelial lesion (LSIL) include repeat cytological testing or colposcopy. However, follow-up cytological studies have usually had high rates of loss to follow-up, a 53% to 76% likelihood of abnormal follow-up cytology results requiring eventual colposcopy, and a small but real risk of delaying the identification of invasive cancers.
- Disadvantages of colposcopy are those previously outlined above for women with ASC, but they appear to be outweighed by the higher risk of abnormality in women with LSIL. Even in patients found to have biopsy-confirmed CIN 1, establishing a histopathologically confirmed diagnosis as merit since it allows a treatment plan to be developed based on knowledge of the patient´s cervical lesion.
- Several approaches, including HPV DNA testing and loop electrosurgical excision procedures, do not appear to be useful for the initial management of women with LSIL
- Receiver operator curve analysis evaluating the performance of HPV DNA testing for the detection of women with CIN 2,3 has reported a lower specificity at a given level of sensitivity among women being evaluated for LSIL, compared with those being evaluated for ASC. Loop electrosurgical excision procedures to excise the transformation zone in women referred for

an abnormal cervical cytology result, but in whom biopsy-confirmed CIN has not been documented, frequently fail to identify neoplasia.

High-grade squamous intraepithelial lesion (HSIL) management

- Women with high-grade squamous intraepithelial lesion (HSIL) in whom a high-grade cervical or vaginal lesion is not identified after colposcopy appear to be at considerable risk for having an undiagnosed CIN 2,3 lesion. In some studies, up to 35% of women with a biopsy diagnosis of CIN 1 and a cytological result of HSIL have been found, after additional workup, to have biopsy-confirmed CIN. Therefore, additional steps are usually taken when a high-grade cervical or vaginal lesion is not identified in a woman with HSIL. One of the first steps that is often taken is to perform a careful review of the colposcopic findings, biopsy results, and initial cervical cytology results. Numerous studies have shown that cytopathologists and histopathologists frequently differ in their interpretation of both cytological and histological cervical abnormalities, and that such a review can sometimes resolve the discrepancy.
- Many colposcopists believe that a cytology test result of HSIL in a pregnant patient requires special consideration. Pregnancy accentuates both normal and abnormal colposcopic findings, and clinicians may not obtain appropriate cervical biopsies out of concern of increased bleeding. Although cervical biopsy during pregnancy is associated with an increased risk of minor bleeding, it has not been associated with increased rates of major bleeding or pregnancy loss in the large studies, and a failure to perform cervical biopsies in pregnant women has been associated with missed cancers. Because of the risk of potential injury to the fetus, endocervical sampling is not recommended during pregnancy.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The guidelines should never be a substitute for clinical judgment. Clinicians need to practice clinical discretion when applying a guideline to an individual patient since it is impossible to develop guidelines that apply to all situations.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Wright TC Jr, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA 2002 Apr 24;287(16):2120-9. [89 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2002 Apr 24

GUIDELINE DEVELOPER(S)

American Society for Colposcopy and Cervical Pathology - Medical Specialty Society

GUIDELINE DEVELOPER COMMENT

A panel of 121 experts in the diagnosis and management of cervical cancer precursors, including representatives from 29 professional organizations, federal agencies, and national and international health organizations, were invited to participate in a consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology (ASCCP). Representatives from the following organizations participated in the ASCCP Consensus Conference held in Bethesda, MD: Agency for Healthcare Research and Quality, American Academy of Family Physicians, American Cancer Society, American College Health Association, American College of Obstetricians and Gynecologists, American Medical Women's Association, American Social Health Association, American Society for Clinical Pathologists, American Society for Colposcopy and Cervical Pathology, American Society of Cytopathology, Association of Reproductive Health Professionals, Centers for Disease Control and Prevention, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Division of Laboratory Systems, Centers for Medicaid and Medicare Services, College of American Pathologists, Eurogin, Food and Drug Administration, International Academy of Cytology, International Federation for Cervical Pathology and Colposcopy, International Gynecologic Cancer Society, International Society of Gynecological Pathologists, National Cancer Institute, National Association of Nurse Practitioners in Women's Health, Papanicolaou Society, Pan American Health Organization, Planned Parenthood Federation of America, Society of Canadian Colposcopists, Society of Gynecologic Oncologists, Society of Obstetricians & Gynaecologists of Canada.

SOURCE(S) OF FUNDING

These guidelines were developed with support from the American Society of Colposcopy and Cervical Pathology and by National Cancer Institute grant 1 R13 CA 96190-01. No industry funding was used.

GUIDELINE COMMITTEE

- Atypical Squamous Cells of Undetermined Significance (ASCUS) Working Group
- Atypical Glandular Cells of Undetermined Significance (AGUS) Working Group
- Low-grade Squamous Intraepithelial Lesions (LSIL) Working Group
- High-grade Squamous Intraepithelial Lesions (HSIL) Working Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Primary Authors: Thomas C. Wright, Jr, MD; J. Thomas Cox, MD; L. Stewart Massad, MD; Leo B. Twiggs, MD; Edward J. Wilkinson, MD

ASCUS Working Group: Thomas C. Wright, MD*; Walter Kinney, MD*; Barbara Apgar, MD; Carmel Cohen, MD; Hershel Lawson, MD; Mark Schiffman, MD, MPH; Mark Sherman, MD; Pamela Stratton, MD; Cornelia Trimble, MD; Leslie Walton, MD

AGUS Working Group: J. Thomas Cox, MD*; R. Marshall Austin, MD, PhD*; Raheela Ashfaq, MD; Francisco Garcia, MD, MPH; Diane Harper, MD, MPH; Kenneth Noller, MD; Thomas Purdon, MD; Ellen Sheets, MD; Ted Trimble, MD, MPH; Ralph Richart, MD; V. Cecil Wright, MD

LSIL Working Group: Edward Wilkinson, MD*; Kenneth Hatch, MD*; Marluce Bibbo, MD; Terrance Colgan, MD; Terri Cornelison, MD; Daron Ferris, MD; Edward Partridge, MD; Mark Spitzer, MD; Claudia Werner, MD; Alan Waxman, MD

HSIL Working Group: Leo Twiggs, MD*; Jay Carlson, DO*; J. L. Benedet, MD; Christopher P. Crum, MD; Juan Felix, MD; Verda Hunter, MD; Burton Krumholz, MD; Neal Lonky, MD, MPH; L. Stewart Massad, MD; Luis Padilla, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Dr. Wright was the principal investigator of clinical trials investigating human papillomavirus (HPV) DNA testing and liquid-based cytology, funded by Digene Corp and Cytyc Corp via formal grants to Columbia University. Dr. Wright has no financial or equity interest in, ongoing consultancy with, or membership on the scientific advisory board of Digene Corp, which makes the only FDA-approved HPV DNA test in the United States. Dr. Wright currently serves on the speakers bureaus of Cytyc Corp and Tripath Inc, makers of liquid-based cytology test kits. Dr. Cox has previously consulted for Digene Diagnostics and has been on the Digene speakers bureau. He is also a consultant for 3M Pharmaceuticals, Cytyc Corp, and Merck, and is on the speakers bureau for 3M Pharmaceuticals and Cytyc Corp. He has no other financial interest in any company that might benefit from cervical screening guidelines. Dr. Massad was formerly the principal investigator

of a grant to the Hektoen Institute correlating cervical disease with fluorescence data for SpectRx Inc. Dr. Twiggs currently serves on the speakers bureaus for Cytyc Corp and Tripath Inc. Dr. Wilkinson serves as a consultant for SpectRx and Welch Allyn, and is on the speakers bureau of Cytyc Corp.

Dr. Apgar has served on the speakers bureau of TriPath Imaging, Inc.; Dr. Ashfaq has received honoraria and travel expenses for lectures from Cytyc Corp.; Dr. Austin has been a speaker or consultant without personal compensation for AutoCyte, Inc., Cytyc, Digene Corp., Morphometrics, NeoPath, Inc., Neuromedical Sciences, Inc., and Veracel, Inc.; Dr. Colgan has been a principal investigator for NeoPath and AutoCyte, and has served as a consultant for Veracel; Dr. Ferris has received honoraria from Cytyc and Digene, grants from Cytyc, and has served as a consultant for Digene; Dr. Garcia has received research supplies from Cytyc and Digene, but has no financial intereste in either; Dr. Hunter has served on the speakers bureau of USHealthConnect and has served as principal investigator for a pilot study from LifeSpex, Inc.; Dr. Kinney has received laboratory support and supplies from Cytyc and Digene (ending in 1997) for a study of ASCUS, and has served on the speakers bureaus of Cytyc and Digene; Dr. Krumholz has served on the speakers bureau of Cytyc; Dr. Lonky is the Chairman of the Medical Advisory Board of, and is a shareholder and Director of, Trylon Corp., and has served on the speakers bureau of 3M Corp.; Dr. Richart has served on the speakers bureaus of Cytyc and Digene, and is a shareholder of Digene common stock; Dr. Sheets has served on the speakers bureau of Cytyc; Dr. Sherman has received research support from Cytyc and Digene; Dr. Spitzer has served on the speakers bureaus of 3M, Cytyc, and USHealthConnect, and has received research support from Polartechnics Corp.; Dr. Walton owns shares of Cytyc, and has received a Pap smear grant funded by Digene.

GUIDELINE STATUS

This is the current release of the guideline. This guideline updates the following previously issued guidelines:

- Management guidelines for follow-up of atypical squamous cells of undetermined significance (ASCUS). Colposcopist 1996 Winter;27(1):1-9.
- Endocervical curettage. J Lower Genital Tract Disease 1997;1(4):251-6.
- Management issues related to quality of the smear. J Lower Genital Tract Disease 1997;1(2):100-6
- Management of glandular abnormalities in the cervical smear. J Lower Genital Tract Disease 1997;1(1):41-5.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society of Colposcopy and Cervical Pathology (ASCCP) Web site. Also available online from the Journal of the American Medical Association (JAMA).

Print copies: Available from the American Society of Colposcopy and Cervical Pathology National Office, 20 West Washington St, Suite 1, Hagerstown, MD 21740.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Definitions of Terms Utilized in the Consensus Guidelines
- Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC- US)
- Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC- US) In Special Circumstances
- Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC - H)
- Management of Women with Atypical Glandular Cells (AGC)
- Management of Women with Low- grade Squamous Intraepithelial Lesions (LSIL)
- Management of Women with Low- grade Squamous Intraepithelial Lesions In Special Circumstances
- Management of Women with Low- grade Squamous Intraepithelial Lesions In Special Circumstances
- Management of Women with High- grade Squamous Intraepithelial Lesions (HSIL)

Electronic copies: Available in Portable Document Format (PDF) from the American Society of Colposcopy and Cervical Pathology (ASCCP) Web site.

Print copies: Available from the ASCCP National Office, 20 West Washington St, Suite 1, Hagerstown, MD 21740.

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 13, 2002. This summary was updated by ECRI on September 13, 2002. It was verified by the guideline developer on November 19, 2002.

COPYRIGHT STATEMENT

Date Modified: 4/12/2004


FIRSTGOV